REMARKS/ARGUMENTS

By this Amendment, claims 27, and 47-50 are amended, claims 51-56 are added, and claims 28-29, 33 are cancelled. Claims 39-45 have been withdrawn from consideration pursuant to a restriction requirement. Claims 27, and 30-32, 34-50 are pending.

Citations to the Specification are directed to U.S. Patent Application Publication No. 2006/0240050 (Surman et al.). Support for the amendments to the claims can be found throughout the Specification as filed, and specifically: support for the limitation "wherein the wetting agent is present in an amount of between about 0.1% and about 15%" can be found in ¶[0014]; support for the limitation "wherein the wetting agent is selected from any one or more of propylene glycol, glycerin, and polyethylene glycol" can be found in ¶[0015]; support for the limitation "wherein the composition comprises: clozapine, glycerin, sodium dihydrogen phosphate dihydrate/NaOH buffer, xanthan gum, sodium methyl paraben, sodium propyl paraben and water" can be found in ¶[0026] to ¶[0045]; support for the limitation "wherein the composition comprises: clozapine, glycerin, xanthan gum, sodium methyl paraben, sodium propyl paraben and water" can be found in ¶[0026] to ¶[0045]; support for the limitation "wherein the composition is stable for at least 14 months" can be found in ¶[0167]. No new matter has been added by this amendment.

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

Interview

The Examiner's courtesy in granting an interview to Applicant's representative on January 25, 2011 is gratefully acknowledged. Applicants' separate record of the substance of the interview is incorporated into the following remarks.

Rejection under 35 USC § 102

Claims 27, 30-33, 35-36, and 47-48 stand rejected under 35 U.S.C. 102(b) as being anticipated by Eishun (JP 10-175865). This rejection is respectfully traversed.

The Examiner sets forth that the Eishun reference teaches formulations for eye drops and argues that while the claims recite a composition, the intended use recited in the preamble would reasonably appear not to be a claim limitation. The Examiner argues that the intended use of oral

administration in the composition claims is met by the prior art, because the prior art compositions would be at least capable of performing said use.

The Examiner argues that clozapine is practically insoluble in water, and that the Eishun's composition could not be a true solution, but rather is a suspension. The Examiner argues that Eishun disclosed filtering the composition, which would avoid the few particles which are large enough to cause irritation.

In Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987) (MPEP 2131), the CAFC set forth that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference". In the instant case, not every element of the claims is present in the Eishun (JP 10175865) reference.

The claims as amended are directed to a physicochemically stable aqueous composition for oral administration comprising clozapine in suspension, a wetting agent, and a buffer, wherein the pH of the composition is maintained within the range of about 6 to about 11. In contrast to the claimed stable clozapine composition for oral administration, the Eishun reference does not teach or suggest the presence of a wetting agent in the clozapine composition.

The Eishun reference does not teach every element of the claims. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Rejection under 35 USC § 103

Claims 27, 30-38, 47-49 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Eishun (JP 10-175865) in view of Honma et al (US 6,569,903), Ali et al (US 5,521,222) and Horlington (US 4,425,346). This rejection is respectfully traversed.

With regard to Declaration filed on 08/10/2010 which shows an unexpected result with a stability of 2 years, the Examiner finds this argument unpersuasive, allegedly because Applicants' declaration is not commensurate in scope with the breadth of the claims. The Examiner argues that claim 27 recites the pH of 6-11, but the pH of the comparison formulation has a pH of 7.2.

However, the claims are patentable over the combination of Eishun in view of Honma, Ali, and Horlington at least for the following reasons. The framework for the objective analysis for determining obviousness under 35 U.S.C. 103 is stated in *Graham v. John Deere Co.*, 383

U.S. 1, 148 USPQ 459 (1966). Obviousness is a question of law based on underlying factual inquiries. The factual inquiries enunciated by the Court are as follows: (A) Determining the scope and content of the prior art; and (B) Ascertaining the differences between the claimed invention and the prior art; and (C) Resolving the level of ordinary skill in the pertinent art. To establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385 (CCPA 1970). MPEP 2143.03. It is important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. (*KSR v Teleflex*, 12 S.Ct. 1727, 1740 (US 2007)).

The instant claims are directed to a physicochemically stable aqueous composition for oral administration comprising clozapine in suspension, a wetting agent, and a buffer, wherein the pH of the composition is maintained within the range of about 6 to about 11.

As set forth in the response filed August 10, 2010, the Eishun reference is not practical for making an oral solution, and the deficiencies of the Eishun reference are not addressed by the combination with the Honma, Ali, and Horlington references, because the instant claims are directed to stable oral formulations of clozapine, and further comprising a wetting agent. The cited references teach formulations for either eye drops/eye gel or ointment. In these references, clozapine (at levels between 0.0001 and 5%, more likely 0.1 to 0.5%) is dissolved in 0.9% NaCl solution. Clozapine is dissolved in 0.9% sodium chloride solution and then added to a viscosity modifier. These are not true suspensions in which clozapine particles are suspended in a matrix.

The Honma reference discloses an ophthalmic composition (see '903 at col. 2. lines 16-22, emphasis added). Accordingly, the Honma reference does not teach or suggest an oral suspension formulation of clozapine, comprising a wetting agent.

With regard to the Ali patent, it discloses ophthalmic pharmaceutical vehicles (see '222 at col. 1, lines 40-46, emphasis added). Accordingly, the Ali patent does not teach or suggest an oral clozapine suspension formulation, comprising a wetting agent.

The deficiency of the Eishun, Honma and Ali patents are not cured by combination with the Horlington patent. The Horlington patent discloses an agent which could be applied topically to treat ocular hypertension and glaucoma (see '346 at col. 1, lines 18-25, emphasis added). The

Horlington patent does not teach or suggest an oral formulation of clozapine in suspension, comprising a wetting agent.

In addition, since none of the Eishun, Honma, Ali, Horlington references disclose or suggest a physicochemically stable aqueous composition for oral administration comprising clozapine in suspension, a wetting agent, and a buffer, wherein the pH of the composition is maintained within the range of about 6 to about 11, the combination of the patents does not and cannot disclose or suggest these limitations.

Furthermore, there is no motivation for one of skill in the art to alter the teachings of the Eishun reference or the Honma, Ali, or Horlington patents to arrive at the claimed method, and no reasonable expectation of success. The combination of the Eishun reference and the Honma, Ali, or Horlington patents does not teach or suggest all the claim limitations, specifically the combination does not teach or suggest stable oral suspension formulations of clozapine, and therefore, since the combination of the references does not disclose or suggest these limitations, there is no motivation to combine the references to reach these limitations, and no expectation of success.

Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Rejection under 35 USC § 103

Pending claims 27, 30-34, 36-38, 46-50 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Ramuth et al (Pharm J 1996; 257: 190-1) as evidenced by Walker *et al.* (Canadian J Hospital Pharmacy. 58:5. (2005) in view of Remington (Remington: The Science and Practice of Pharmacy 20th edition (2000); pg. 245 and 273-274) and Eishun (JP 10-175865).

The Examiner argues that Ramuth teaches a clozapine suspension composition comprised of: 1000 mg of clozapine in 50rnL of Guy's hospital formula base solution (see pg. 190, under Preparation of clozapine suspension), which would be a 2% concentration. The Guy's hospital formula base contains: syrup, which would read on sweetener; methyl hydroxybenzoate, which is methylparaben; and carboxymethylcellulose, which is a thickening/suspending agent. No tests for microbiological stability have been performed on the suspension, but the suspension is considered stable for at least 18 days.

The Examiner admits that Ramuth does not teach using a buffer system of sodium phosphate/sodium hydroxide for a pH of 6-8; or a wetting agent; such as propylene glycol or glycerin.

The Examiner argues that Walker disclosed that oral suspensions of clozapine in Ora-Sweet, Ora-Plus, simple syrup, or Guy's pediatric mixture (the vehicle discussed in Ramuth) are able to retain more that 95% of the initial concentration for 63 days. The stability end point was not determined. The Examiner argues that Remington teaches optimization of pH and buffer for drug stabilization. The Examiner argues that Eishun teaches common pH buffer systems include sodium phosphate.

The Examiner admits that the references do not specifically mention optimizing pH as claimed, but argues that the pH of a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize using a buffer system, such as sodium phosphate.

However, the claims are patentable over the combination of Ramuth, Walker, Remington, and Eishun at least for the following reasons. The amended claims are directed to a physicochemically stable aqueous composition for oral administration comprising clozapine in suspension, a wetting agent, and a buffer, wherein the pH of the composition is maintained within the range of about 6 to about 11.

The Ramuth reference discusses compounding clozapine into liquid preparations using Guy's Pediatric Base, however, the reference only tested stability for 18 days, as opposed to the at least 14 month stability, as has been shown for the claimed composition. The instant Specification teaches that clozapine in such typical solutions is readily susceptible to hydrolysis (see ¶[0006]). In addition, as the Examiner has admitted, the Ramuth reference does not teach or suggest compositions comprising a wetting agent. These deficiencies are not cured by the combination of the Walker, Remington, or Eishun references.

None of the Walker, Remington, or Eishun references teach or suggest a stable formulation of clozapine which comprises a wetting agent. Since none of the Ramuth, Walker, Remington, or Eishun references disclose or suggest a physicochemically stable aqueous composition for oral administration comprising clozapine in suspension, a wetting agent, and a buffer, wherein the pH of the composition is maintained within the range of about 6 to about 11,

the combination of the patents does not and cannot disclose or suggest these limitations. Additionally, since the combination of the references does not disclose or suggest these limitations, there is no motivation to combine the references to reach these limitations, and no expectation of success.

* * *

For at least the reasons set forth above, it is respectfully submitted that the above-identified application is in condition for allowance. Favorable reconsideration and prompt allowance of the claims are respectfully requested.

Should the Examiner believe that anything further is desirable in order to place the application in even better condition for allowance, the Examiner is invited to contact Applicant's undersigned attorney at the telephone number listed below.

Respectfully submitted,

CAESAR, RIVISE, BERNSTEIN,
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Please charge or credit our Account No. 03-0075 as necessary to effect entry and/or ensure consideration of this submission.